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Title	:	IMIDAZOTRIAZINONE DERIVATIVES AS PDE 7 INHIBITORS	
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SUBMISSION OF REPLACEMENT SHEETS OF TRANSLATION OF PRIORITY DOCUMENT

Sir:

Enclosed please find replacement sheets for pages 3, 4, 17 and 20 of the translation of Japanese Application No. JP 2003-170095, the priority document for the above-captioned application.

Applicants believe that no fee is required for the submission of the replacement sheets for the translation of the priority document. However, in the event that a fee is required to enter this submission, please charge such fee to the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,
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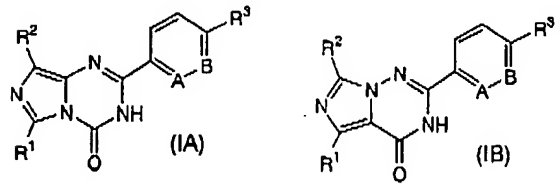
【Name of the Document】 DESCRIPTION

【Name of the Invention】 IMIDAZOTRIAZINONE DERIVATIVES AS PDE 7 INHIBITORS

【Claims】

【Claim 1】 An imidazotriazinone compound represented by the following formula (IA) or (IB):

【Formula 1】



wherein

A is N or CR^4;

B is N or CH;

R^1 is substituted or unsubstituted cycloalkyl group or tert-butyl group;

R^2 is a hydrogen atom or C_1-C_6 alkyl group;

R^3 is a hydrogen atom; a halogen atom; nitro group; cyano group; heteroaryl group; substituted or unsubstituted C_1-C_6 alkyl group; substituted or unsubstituted C_2-C_6 alkenyl group; saturated or unsaturated heterocycloalkyl group; a group: $-NR^5R^6$, $-C(O)R^7$, $-SO_2R^7$, $-OR^8$, $-NR^8COR^7$, $-NR^8SO_2R^7$;

R^4 is a hydrogen atom or C_1-C_3 alkoxy group which is unsubstituted or substituted by one or more fluorine atom(s);

R^5 and R^6 are, same or different from each other, a hydrogen atom; substituted or unsubstituted C_1-C_6 alkyl group; substituted or unsubstituted acyl group which is substituted or unsubstituted; or substituted or unsubstituted heterocycloalkyl group;

R^7 is a hydrogen atom; substituted or unsubstituted C_1-C_6 alkyl group; substituted or unsubstituted heterocycloalkyl group; OH; $-OR^8$ or $-NR^5R^6$;

R^8 is a hydrogen atom, substituted or unsubstituted C_1-C_6 alkyl group; or substituted or unsubstituted heterocycloalkyl group;

or pharmaceutically acceptable salts or solvates thereof.

【Claim 2】 The compound represented by the formula (IA) according to claim 1.

【Claim 3】 The compound represented by the formula (IB) according to claim 1.

【Claim 4】 The compound according to claim 1, 2 or 3, in which

R^1 is substituted or unsubstituted C_3-C_8 cycloalkyl group.

【Claim 5】 The compound according to claim 4, in which R^1 is selected from the group consisting of cyclopentyl, cyclohexyl and cycloheptyl .

【Claim 6】 The compound according to any one of claims 1 to 5, in which A is CR^4 wherein R^4 is methoxy or ethoxy group.

【Claim 7】 The compound according to any one of claims 1 to 6, in which B is CH.

【Claim 8】 The compound according to any one of claims 1 to 7, in which R^2 is methyl group.

【Claim 9】 The compound according to any one of claims 1 to 8, in which R^3 is a haydrogen atom; a halogen atom; saturated or unsaturated heterocycloalkyl group; group selected from the $-NR^5R^6$, $-C(O)R^7$, and $-SO_2R^7$, wherein R^7 is OH, $-OR^8$, $-NR^5R^6$ and substituted or unsubstituted heterocycloalkyl group.

【Claim 10】 A pharmaceutical composition containing a compound according to any one of claims 1 to 9, or pharmaceutically acceptable salts or solvates thereof as active ingredient.

【Claim 11】 A PDE 7 inhibitor containing a compound according to any one of claims 1 to 9, or pharmaceutically acceptable salts or solvates thereof as active ingredient.

【Detailed Description of the Invention】

【0001】

【Technical Field】

The present invention relates to imidazotriazinone derivatives, pharmaceutically acceptable salts and solvate thereof, and having selective PDE 7 (phosphodiesterase VII) inhibiting effect. These compounds are effective compounds for treating various kinds of disease such as allergic disease, inflammatory disease and immunologic disease.

【0002】

【Background Art】

A cyclic AMP (cAMP) or cyclic GMP (cGMP), which is an intracellular second messenger substance, is decomposed and inactivated by phosphodiesterase (PDE 1 to PDE 11). The PDE 7 selectively decomposes cAMP, and is characterized as an enzyme not decomposed by rolipram. Rolipram is a selective inhibitor of PDE 4 which decomposes cAMP.

【0003】

It is suggested that PDE 7 plays an important role for activating

【0045】

(wherein, A, B, R^1, R^2 and R^3 have same meaning mentioned above; L is C_1-C_3 lower alkyl, and Z' is halogen atom, preferably chlorine atom.)

【0046】

The compound (IB) of the present invention can be obtained in accordance with the known method (e.g., Japanese Patent Publication No. 2001-522851). That is, the compound (X) is obtained by the reaction of the compound (XI) with the compound (XIV). This reaction can be conducted in ethers solvent such as tetrahydrofuran, in the presence of organic base such as pyridine or triethylamine, and catalyst such as 4-dimethylaminopyridine, at 0°C to reflux temperature. Separately, the compound (XII) is obtained from the compound (XIII) by reacting hydrazine hydrate in alcohols solvent at 0°C to reflux temperature. Then, the compound (IX) is obtained by reacting the above compound (X) with the compound (XII) in alcohols solvent such as ethanol at room temperature to reflux temperature. Finally, the purpose compound (IB) is obtained by the reaction of the compound (IX) with phosphorus oxychloride in a halogenated hydrocarbon such as 1,2-dichloromethane or chloroform.

【0047】

After the reaction is completed, the solvent is neutralized by adding inorganic base aqueous solution such as sodium hydrogen carbonate aqueous solution, and the mixture is extracted with the organic solvent, which is nonmiscible solvent with water. The extracted organic layer is washed sequentially with water and saturated saline solution, then, the solvent is removed to give the purpose compound (IB). The compounds (XI), (XIV) and (XIII) to be used in this reaction can be commercially available or known compounds. Further, the compound (XIII) to be used in this reaction can also be prepared in accordance with the known method (e.g., Japanese Patent Publication No. 2001-522851).

【0048】

All reaction mentioned above are well known, and the reagents to be used or the reaction conditions to be applied can be easily established in accordance with the standard text book and the examples mentioned later. Therefore, the other methods or modified methods for obtaining the compound (IB) of the present invention can be easily selected by the person skilled in the art in this field.

【0049】

【Example】

invention caused by PDE 4 to be less.

【0062】

The selectivity against PDE 4 (phosphodiesterase IV) of the compounds of the present invention was affirmed by means of the following Biological Test.

【0063】

Biological Test 2:

Methods for evaluating the PDE 4 inhibiting effect

The PDE 4 (phosphodiesterase IV) inhibiting effect of the compounds of the present invention was performed by the following method, which was modified assay method described in *Biochemical. Pharmacol.* 48(6), 1219-1223 (1994).

【0064】

(1) The active fraction of PDE 4 was obtained. That is, the livers obtained from three Balb/c mice (male, 12 weeks: obtainable from CLEA Japan, Inc.) were suspended with 30mL of buffer solution B [20mM of bis-tris, 5mM of 2-mercaptoethnol, 2mM of benzamidine, 2mM of EDTA, 0.1mM of 4-(2-aminoethyl)benzensulfonyl hydrochloride, 50mM of sodium acetate; pH 6.5], then homogenized by Polytron® homogenizer. The homogenate were centrifuged under 25,000 × G for 10 minutes at 4° C. The supernatant was separated and thus obtained supernatant was further centrifuged under 100,000 × G for 60 minutes at 4° C, and then filtrated with 0.2μm filter to obtain the soluble fraction.

【0065】

(2) The obtained soluble fraction was filled in equilibrium DEAE sepharose column (1 × 10cm) with buffer solution B, and phosphodiesterase fractions were eluted by 120mL of buffer solution B with linear gradient from 0.05 to 1M sodium acetate concentration. 5 ml each of 24 eluents were collected, and each eluents were examined for cyclic AMP metabolic activities of phosphodiesterase. The fraction eluting with about 620mM of sodium acetate concentration parts, where metabolic activities were inactivated by 30μM of rolipram (selective inhibitor for phosphodiesterase IV), were collected as storage solution to test PDE 4 inhibiting effect.

【0066】

(3) The tested compound having desired concentration was reacted in the solution of 20mM tris-HCl (pH 7.5), 1mM of $MgCl_2$, 100μM of EDTA, 330μg/mL of bovine serum albumin, 4μg/mL of 5'-nucleotidase, 0.1μCi of ^{3}H-cAMP (0.064μM of cAMP), and storage solution of PDE 4 for 2 hours at 25° C. After the reaction, suspension of Sephadex®-QAE in 10mM of